The Selenium Dilemma

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Selenium is an essential nutrient and at low dietary levels has been shown to prevent death from deficiency in a variety of species. At high dietary levels selenium is extremely toxic, and has been reported to be carcinogenic.

These findings are of grave importance to our national health. They are not to be treated emotionally or politically. The evidence must be carefully assessed by competent scientists using unbiased scientific analysis. A basis for action must be reached which will provide for the nutritional needs of man and animals, and at the same time prevent the occurrence of toxic levels of this element in foods and feeds.

Selenium was discovered by the Swedish chemist Berzelius (1) over 150 years ago as an atomic element closely associated with sulfur and tellurium. The toxicity of selenium has been known since 1934, when Franke (2) indicated that the high levels of selenium in plant foodstuffs of South Dakota were responsible for alkali disease in cattle and other livestock. This disease is characterized by loss of hair, sloughing off of hooves and nails, loss of teeth and a particular kind of paralysis. Selenium toxicity causes reproductive failure, and chick and mammalian embryos show peculiar malformations (3–5).

A nutritional requirement for selenium was unsuspected until 1957 when Schwarz and Foltz (6) found that 0.1 ppm of selenium in the diet of vitamin E-deficient rats completely prevented dietary liver necrosis. Since then selenium has been demonstrated to be an important factor in the nutrition and normal metabolism of chickens, turkeys, pigs, cattle, sheep and other animals. Selenium is more effective than vitamin E in preventing exudative diathesis in chicks (7, 8), white muscle disease in lambs [1] (9) and calves (10, 11) and liver necrosis in pigs (12, 13). Administration of selenium as sodium selenite has been reported also to increase growth in children with kwashiorkor (14, 15).

Most early nutritional studies with laboratory animals and livestock indicated that selenium simply had a sparing effect upon the vitamin E requirements of animals. However, recent studies using amino acid basal diets severely deficient in selenium, and chicks from selenium-depleted hens have shown that selenium is a required nutrient per se (16). Chicks fed the selenium-free diet showed severe degeneration and fibrosis of the pancreas even when the diet was supplemented with all nutrients known to be required, including high levels of vitamin E. Addition of as little as 0.02 ppm of selenium to this basal diet completely prevented pancreatic fibrosis and promoted growth. Research at Oregon State University (17) has provided evidence that selenium also is an essenial nutrient for rats. Although rats fed low selenium diets supplemented with 60 mg of *d*-α-tocopheryl acetate per kilogram grew and reproduced normally, their offspring receiving the same diet were almost hairless, grew slowly and failed to reproduce. Addition of 0.1 mg of selenium per kilogram of diet restored the hair, growth and reproductive ability in these second generation rats.

Recent research at the University of Wisconsin (18) has shown that selenium par-

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[1] Proctor, J. F., D. E. Hogue and R. G. Warner 1958 Selenium, vitamin E and linseed oil meal as preventives of muscular dystrophy in lambs. J. Anim. Sci. *17:* 1183 (abstr.).

ticipates in the activity of the glutathione peroxidase of rat erythrocytes. These findings have been extended in the author's laboratory [2] where it has been found that the glutathione peroxidase of chick plasma is high in chicks receiving selenium, but drops to a low level in selenium-deficient chicks just prior to onset of exudative diathesis.

Several interesting interrelationships have been discovered concerning toxicities of cadmium, mercury, thallium, arsenic and selenium. These effects appear to be concerned with the influence of one or more of these elements upon the rate or mode of excretion of the others (19, 20). Work by Mason and Young (21) has shown that selenium is approximately one hundred times as effective as zinc in preventing the injury to the testes of rats produced by injection of cadmium chloride.

Problems of selenium deficiency in commercial poultry and livestock. Numerous cases of selenium deficiency have occurred in poultry and livestock on farms in those areas of the world where the selenium content of the soil is low, and therefore the local feeds and forages contain insufficient selenium to meet the nutritional requirements of the animals. The first recognized field case of selenium deficiency occurred in a large flock of turkeys in Ohio. Myopathies of the gizzard and heart resulted in severe mortality in the turkeys at approximately 5 to 6 weeks of age. The problem was found to be due to the very low level of selenium in both the corn and the soybean meal produced in Ohio (22). Subsequently, numerous flocks of turkeys and broilers throughout the eastern half of the United States have suffered poor growth, poor efficiency of feed utilization, and high mortality shown to be due to deficiency of selenium in the feeds fed to these flocks.

In lambs and calves, nutritional muscular dystrophy, recognized as an endemic disease in New York State and other areas of the eastern United States for half a century, can now be controlled by supplementing the diet of the pregnant cow or ewe with approximately 0.1 mg selenium per kilogram of total diet. This level of selenium also will prevent exudative diathesis in chicks; however, the studies with turkeys indicated that 0.2 mg selenium as sodium selenite is needed per kilogram of practical diets to completely prevent heart and gizzard myopathy in young poults.

The very high incidence of selenium deficiency in the eastern part of the United States appears to be due not only to the low selenium content of the feedstuffs but also to a very low biological availability of selenium in many feedstuffs, averaging approximately 85% for grains, 65% for soybean meal, but only 33% for fish meal, meat scraps and other products of animal origin.[3]

The studies referred to above, and numerous other investigations, demonstrate that selenium is an essential nutrient. The studies have shown further that many commercial diets for poultry and livestock are severely deficient in selenium. A review of the voluminous literature demonstrating the need for selenium supplementation of many commercial poultry and livestock feeds has been published by the National Academy of Sciences. The review was made by a seven-member subcommittee on selenium acting for the Committee on Animal Nutrition of the National Research Council. This publication, entitled, "Selenium in Nutrition," describes the overwhelming evidence for the need to supplement many commercial poultry and livestock feeds with selenium.

On March 9, 1970, the American Feed Manufacturers Association submitted a formal request [4] to the Food and Drug Administration for approval to add sodium selenite or sodium selenate to feeds for chickens, turkeys and swine in amounts not to exceed 0.25 ppm total Se in feeds for chickens and swine, and 0.35 ppm in feeds for turkeys. It was requested that the additive be incorporated into feeds as a premix containing a suitable marker for qualitative control identification and that these premixes be labeled to identify the form of selenium additive used and the quantity of selenium present. Request was made also that the finished feeds be labeled to bear the name of the form of selenium which had been added to the feed.

The Food and Drug Administration officials requested information on tissue levels

[2] Scott, M. L., and T. Noguchi 1973 Metabolic function of selenium in prevention of exudative diathesis in chicks. Federation Proc. *32:* 3747 (abstr.).
[3] Cantor, A. H., and M. L. Scott 1972 Biological availability of selenium in several feedstuffs of plant and animal origin. Poultry Sci. *51:* 1790 (abstr.).
[4] Number MF-3433-V, amended May 12, 1971.

of selenium in broilers, turkeys and swine fed graded levels of selenium below and somewhat above the nutritional requirements. Studies by Cantor and Scott [5] demonstrated that the selenium content of the blood and muscle of broilers and turkeys did not increase when dietary selenium levels were increased from 0.2 to 0.8 ppm. Ullrey [6] obtained similar results with swine. The maximum blood levels observed with 0.8 ppm of selenium in the diets of broilers or turkeys was no higher than 0.25 ppm. This is the average selenium value found by Allaway et al. (23) in the blood of human blood donors in Rapid City, South Dakota, where the selenium content of the soil and therefore of local vegetables, meats and milk is about as high as in any other locale in the United States.

As a result of these findings, the Food and Drug Administration published in the Federal Register for June 17, 1971, the Notice of Filing of the AFMA petition. However, to this date, because of the legislation under which the Food and Drug Administration must operate, final approval has not been given for the addition of nutritional levels of selenium to animal feeds.

In the meantime, almost all feed manufacturers in the northeastern United States have reported case after case of severe selenium deficiency in broilers and turkeys receiving their feeds. Veterinarians in the New York State Diagnostic Laboratories have encountered numerous flocks of broilers and turkeys showing high mortality from exudative diathesis or gizzard and heart myopathies. Growth and efficiency of feed utilization were reduced. These cases responded promptly to "experimental" supplementation of the diet or drinking water with sodium selenite at levels to provide 0.1 to 0.2 mg selenium per kilogram of diet. Losses to poultrymen due to the illegality of adding this nutrient to feeds have been calculated to be millions of dollars per year. Insidious losses due to poor growth and poor efficiency of feed utilization in chronically selenium-deficient animals may be far greater than that due to acute outbreaks of severe selenium deficiency.

The case for the nutritional essentiality of selenium is unquestioned. The need for supplementation of feeds has been proven beyond any doubt. It has been shown that nutritional amounts of selenium can be added to the diets of poultry and swine without increasing the blood or muscle tissue levels of selenium above those found in people and animals living all of their lives in South Dakota, Wyoming and other areas of the United States. Why then are we not adding selenium to feeds? The answer is simple—selenium has been claimed to be a carcinogen.

Cancer studies using toxic levels of selenium. In 1943, Nelson et al. (24) of the Food and Drug Administration reported that 11 out of 53 rats which had been made cirrhotic by feeding a low protein diet developed adenoma or low grade carcinoma in the cirrhotic livers and four others showed advanced adenomatoid hyperplasia after surviving 18 to 24 months on diets containing 5, 7 or 10 mg of selenium per kilogram. No tumors occurred in any of the rats during the first 18 months of the experiment. No tumors occurred in livers that were not cirrhotic. No encapsulation was noted, and no metastases were seen. The authors stated that the tumors observed . . .

> "were very similar to many of the low grade carcinomas of the rat liver seen after the ingestion of *o*-aminoazotoluene, and anyone who has studied a series of the latter tumors will appreciate the difficulty of deciding just when the borderline between nonmalignant and malignant tumor has been passed, and also just when hyperplasia has passed into tumor."

Because the above selenium toxicity study a) was complicated by being produced only in animals suffering for long times from liver cirrhosis; b) did not unequivocally identify the liver disorder as being cancer; and c) was conducted largely with selenium contained in seleniferous feeds and corn and thus the effects observed could not be ascribed definitely to selenium, an elaborate investigation was undertaken at Oregon State University to determine the possible carcinogenicity of selenium. The results of the study were reported by Tinsley and associates (25) and Harr and associates (26). Eight hundred twenty-nine rats were fed various levels of either sodium selenite or sodium selenate ranging from 0.5 to 16 ppm

[5] Cantor, A. H., and M. L. Scott 1972 Effect of dietary supplements of sodium selenite on tissue selenium levels in market age turkeys. Poultry Sci. *51:* 1790 (abstr.).
[6] Ullrey, D. E. 1972 Personal communication.

of selenium. Two hundred seventy-four rats received control diets containing no selenium; 88 rats were given *N*-2-fluorenylacetamide (FFA), a known hepatocarcinogen. Of the total number of rats started, 175 lived 2 years or more.

One thousand, one hundred twenty-six rats were autopsied in the course of the experiment. Sixty-three neoplasms were found. Forty-three of these occurred in 88 rats fed the carcinogen, FFA. Eleven neoplasms occurred in the 274 rats receiving the control diets; 9 neoplasms were found in the 829 rats that had received selenium at levels ranging from 0.5 to 16 ppm. None of these rats showed hepatic neoplasms. The Oregon workers did find hyperplastic lesions in the livers of about 50% of the selenium-fed rats which lived 282 days or longer. The liver cells were sometimes three to five times normal size and contained multiple nuclei and chromatin granules. The surfaces of the livers were mottled, with pale yellow or white areas. Hydrothorax, ascites, pericardial edema and icterus were common. Chronic toxic hepatitis occurred in many of the rats receiving selenium at 2 ppm or more. These livers showed 1) small hobnailed surfaces; 2) irregular mottled surface; and 3) diffusely enlarged liver. Fibroblastic proliferation occurred around the central vein. Bile duct cell proliferation formed cystic ducts, multiple ducts with fine chains of cells which extended between and into the hepatic lobules. Reticuloendothelial proliferation formed small granulomas around Glisson's Islands.

Thus, although toxic levels of selenium were found by these workers to produce drastic changes in liver and other organs of rats, this element even at high levels did not produce cancer.

At this point the controversy appeared to center on the ability of the researcher to distinguish between hyperplasia and true tumor cell development. The Oregon workers used a recognized hepatocarcinogen to produce cancer in 43 rats. Their investigation, sponsored by the National Cancer Institute, was done with the express purpose of determining whether or not the toxic effects of selenium levels on liver do indeed lead to cancer. Under the conditions of their experiments they found that dietary selenium, as either sodium selenite or sodium selenate, did not produce cancer of the liver in rats.

Several possibilities may explain the differences between the Oregon studies and those of Nelson and associates: 1) Nelson and associates used the Osborne-Mendel strain of rats while the Oregon investigators used the Wistar strain; it is possible that conflicting results were due to genetic differences. 2) While the Oregon workers fed sodium selenite or sodium selenate to provide the levels of dietary selenium, the Nelson group used various levels of seleniferous corn and wheat to provide the selenium levels in most of their work. They did, however, report tumors in two rats which had received 10 ppm of selenium in a mixture of ammonium potassium sulfide and ammonium potassium selenide. They did not feed a control lot ammonium potassium sulfide alone, and they did not have a spectrophotometric analysis of the seleniferous grains to determine whether or not these grains may have been contaminated with a known carcinogen. 3) Nelson et al. reported hepatomas only in rats that also showed cirrhosis. 4) The hyperplasia and "hobnail" appearance of the livers which the Oregon workers observed may have been much more severe in rats already suffering from cirrhosis, thereby forming foci which resembled tumors.

Thus, in 1970, the research work aimed at determining whether or not toxic levels of selenium are carcinogenic stood at one "yes" and one "no." There had been another report from Russia by Volgarev and Tscherkes (27) claiming that in one experiment 10 out of 23 male rats fed 4.3 ppm of selenium had tumors, and in another experiment five out of 19 animals fed 8.6 ppm of selenium showed tumors. This report should be entirely discounted because the Russian workers did not include any control groups of rats which received the basal diet without selenium. An attempt by the Russians to prove that selenium is carcinogenic was thwarted when in a third experiment, in which they included 200 rats fed the control diet, none of the animals in either the control or the selenium-fed groups showed any tumors or precancerous lesions (27).

In 1971 Schroeder and Mitchener (28) reported studies in which 418 Long-Evans strain rats were fed a diet containing whole

rye flour, dried skimmed milk, corn oil and iodized salt plus vitamins and trace minerals. One hundred five rats were fed the basal diet as controls. Sodium selenite and sodium selenate were given in the drinking water to 313 of the rats at a level of 2 mg Se per liter of water for a period of 1 year. The rats showed no signs of tumors after 1 year. At this time the levels of selenite and selenate in the drinking water were increased to 3 ppm of Se. Since most animals drink about 1.5 g of water per gram of dry food intake, this represented a level of approximately 4.5 mg of selenium per kilogram of diet (4.5 ppm). The experiment also was modified at 58 days by the substitution of selenate for selenite in the diet of the male rats because of a high mortality (50%) which had occurred in the selenite-fed males by 58 days of age.

The experiment was further complicated by an epidemic of virulent pneumonia when the rats were 21 months of age. The authors indicated that 38 males and 35 females (total 73 rats) receiving the control diet survived the pneumonia epidemic. Fifty percent of these were dead at 863 days of age. Of the 98 rats that had received selenate, 28 males and 47 females (total 75 rats) survived the pneumonia epidemic. These lived an average of 988 days before they reached 50% mortality.

Of the 73 control rats autopsied after 21 months of age, 20 had tumors, for an incidence of 27.4% in the controls. Thirty tumors were reported in the 75 selenate-fed rats autopsied, or a 40% incidence. In the selenite group only four rats were found to have tumors out of a total of 51 selenite-fed rats autopsied (approximately 8% incidence).[7]

These workers reported that the 8% incidence of tumors in the selenite group was not significantly lower than the 27.4% incidence in the controls, while they claimed that the 40% incidence in the selenate-fed rats represented a significant *increase* in tumors over the 27.4% incidence obtained with the controls.

In their discusion of this subject, Schroeder and Mitchener made much of the age of the rat as an important factor in cancer. They pointed out that only one tumor occurred before 18 months of age. They explained the discrepancy between their results and those of the Oregon workers on the basis that the Oregon workers' animals "did not survive to the tumor-bearing age of 24–39 months or longer, probably because the dose of selenium fed was at the toxic level (4.3 ppm or more in feed), whereas our dose of selenate was at a sub-toxic level."

The level of 3 ppm of selenium as selenate in the drinking water was not toxic to the Long-Evans strain of rats used by Schroeder and Mitchener. Indeed, it appears likely that the beneficial effect of the selenate on longevity of the rats may have been entirely responsible for the higher incidence of tumors observed in the selenate-fed rats as compared to the controls. As indicated above, the selenate-fed rats did not show 50% death from old age until 125 days *after* 50% of the control rats had died.

It is generally considered that 1 month in life-span of a rat is equivalent to approximately 30 months' life-span for man. The 988 days lived by 50% of the selenate-fed rats is equivalent to about 82 years in humans, while 50% of the control rats died at an age equivalent to about 72 years in man. It appears incongruous to point to a substance in the diet which has extended the life span from 72 years to 82 years and claim that this substance is a carcinogen because more individuals in the longer-living group died of cancer. In man and animals alike, it is well attested that if one lives long enough the chances of dying of cancer increase greatly.

Inhibitory effects of selenium on carcinogenesis. In 1949 Clayton and Baumann (29) found that the inclusion in a purified diet of 5 ppm of selenium as sodium selenite reduced the incidence of liver tumors in rats which had previously received the carcinogen *N'*-methyl-*p*-dimethylaminoazobenzene (*N'*-DAB) from 62% in ad libitum-fed controls and 93% in pair-fed controls to 31% in the rats which received selenium.

In 1956 Weisberger and Suhrland (30, 31) found that injection of 1 mg of selenocystine per kilogram of body weight per day for 14 days, following subcutaneous injection of Murphy's lymphosarcoma, reduced the average size of the tumors from an area of approximately 30 cm^2 in the con-

[7] These data were taken from table 4 of reference (28), after correcting an error in the second column, first two lines, where the numbers 75 and 73 appear to be reversed.

trol rats to only 8 cm² in the rats receiving selenium.

Shamberger and Rudolph (32) in 1966 reported on the inhibitory effect of selenium on the cocarcinogenic effect of croton oil. Mice at 55 to 60 days of age were treated with 7,12-dimethylbenzanthracene (125 μg dissolved in acetone). After 21 days, five of these mice were painted five times weekly for 16 weeks with 0.25 ml of a mixture of 0.033% croton oil and 5 ppm of sodium selenide. At the end of 6 weeks there were nine tumors in the animals receiving selenium, whereas there were 132 tumors in the five comparable mice which were painted five times weekly with croton oil in the absence of selenium. Riley in 1968 (33) confirmed these results using the cocarcinogenic principle from croton oil, compound A_1.

Shamberger has recently extended his studies (34). After application of 0.25 ml of 0.03% benzo(*a*)pyrine in acetone for 27 weeks in ICR Swiss mice, it was found that 14 of the 35 mice receiving the control ration had cancers whereas only 8 of 33 mice showed cancers when the diet was supplemented with 1 ppm of sodium selenite.

Lack of correlation between selenium distribution in the USA and human cancer mortality. Because of the inhibitory effects of selenium against a variety of carcinogens in experimental animals, and the possibility that selenium at higher levels might actually be enhancing carcinogenesis, Shamberger and Willis of the Cleveland Clinic Foundation undertook a study (35) to determine whether or not a correlation could be obtained between the level of selenium in the soil, food and tissues of animals and humans, and the published incidence of human cancer mortality in these various areas. Allaway et al. (23) had determined the human blood selenium levels in 19 cities of the United States and had correlated these with the selenium content of the agricultural crops raised in the various areas in which these cities were located. These data were shown by Kubota and Allaway [8] also to correlate with the incidence of selenium deficiency and selenium excess in domestic animals. Shamberger and Willis arranged in descending order the Allaway data for the average selenium content of human blood in the 19 cities. They then recorded the cancer deaths per 100,000 population for each of these cities, as published in the bulletin on Vital Statistics of the United States for the year 1965. The city having the highest selenium blood level was Rapid City, South Dakota, with 0.256 ppm of selenium in the blood. This city showed the *lowest* incidence of cancer deaths—94 per 100,000 population. The city having the lowest average selenium blood level was Lima, Ohio, with 0.157 ppm of selenium. There were 188 deaths from cancer in 1965 per 100,000 population in Lima, Ohio.

Many factors other than selenium content of the blood undoubtedly figured in the cancer mortality in these various cities. Thus this correlation cannot be said to show that higher blood selenium levels *prevent* cancer. It is possible, however, to use these data as evidence that chronic blood selenium values at levels of approximately 0.25 ppm (which was the blood level found by Scott and Thompson (36) to represent the plateau blood level in chicks receiving dietary selenium ranging from 0.2 to 0.8 ppm) *do not increase the incidence of cancer* compared to populations where the selenium of the blood is 0.15 ppm (a level which in chicks and turkey poults verges upon a deficiency).

The work of Shamberger (34) indicates that the level of dietary selenium which had an inhibitory effect on carcinogenesis by croton oil and other chemical carcinogens is somewhat higher than the minimum nutritionally required level of selenium. Shamberger found that Torula yeast diets containing 1 ppm of sodium selenite (approximately 0.5 ppm Se) given to mice markedly decreased the number of skin tumors induced by 7,12-dimethylbenz(α)anthracene plus croton oil and benzo(α)pyramine. Torula diets containing 0.1 ppm of sodium selenite did not decrease tumor incidence.

In summary, selenium has been demonstrated to be a required nutrient. The nutritional requirement lies in the range of 0.1 to 0.3 ppm of selenium. Selenium also is an extremely toxic element. Levels of selenium in the range of 2 to 10 ppm produce a chronic toxicity while levels above 10 ppm produce drastic changes resulting in sudden death.

These studies suggest an inhibitory effect

[8] Kubota, J., and W. H. Allaway 1972 Unpublished results.

of selenium on cancer produced by various carcinogens. The evidence indicating a carcinogenic effect of high doses of selenium is open to question.

The Delaney amendment prohibits the addition to foods and feeds of anything that has been shown to be a carcinogen. The evidence presented in this report indicates a grim possibility. If the experiments reporting a protection against malignant tumors by low doses of selenium are conclusively confirmed, the consequences of restricting the use of selenium at nutritional levels may involve not only the death of untold thousands of chickens, turkeys and pigs from selenium deficiency, but also may be responsible for many deaths from cancer in the human population due to insufficient selenium in many areas of the United States to provide an inhibitory effect upon carcinogenesis.

LITERATURE CITED

1. Berzelius, J. J. 1817 Sur deux métaux nouveaux (litium et sélénium). Schweigger. J. *21:* 1818–23.
2. Franke, K. W. 1934 A new toxicant occurring naturally in certain samples of plant foodstuffs. I. Results obtained in preliminary feeding trials. J. Nutr. *8:* 597–608.
3. Moxon, A. L., and M. Rhian 1943 Selenium poisoning. Physiol. Rev. *23:* 305–337.
4. Rosenfeld, I., and O. A. Beath 1964 Selenium. Geobotany, Biochemistry, Toxicity and Nutrition. Academic Press, New York.
5. Scott, M. L. 1962 Selenium. In: Mineral Metabolism, ed., C. L. Comar and F. Bronner, vol. 2B: 543–558. Academic Press, New York.
6. Schwarz, K., and C. M. Foltz 1957 Selenium as an integral part of factor 3 against necrotic liver degeneration. J. Amer. Chem. Soc. *79:* 3292–3293.
7. Nesheim, M. C., and M. L. Scott 1958 Studies on the nutritive effects of selenium in chicks. J. Nutr. *65:* 601–618.
8. Scott, M. L. 1962 Vitamin E in health and disease of poultry. Vitamins Hormones *20:* 621–632.
9. Muth, O. H., J. E. Oldfield, L. F. Remmert and J. R. Schubert 1958 Effects of selenium and vitamin E on white muscle disease. Science *128:* 1090.
10. Muth, O. H., J. R. Schubert and J. E. Oldfield 1961 White muscle disease (myopathy) in lambs and calves. VII. Etiology and prophylaxis. Amer. J. Vet. Res. *22:* 466–469.
11. Nelson, F. C., M. Hidiroglou nad H. A. Hamilton 1964 The effect of prophylactic treatment of pregnant beef cows on the incidence of nutritional muscular dystrophy. A field trial. Can. Vet. J. *5:* 268–270.
12. Eggert, R. O., E. Patterson, W. T. Akers and E. L. R. Stokstad 1957 The role of vitamin E and selenium in the nutrition of the pig. J. Anim. Sci. *16:* 1037.
13. Grant, C. A., and B. Thafvelin 1958 Selenium and hepatosis diaetetica of pigs. Nord. Vet. Med. (in Swedish) *10:* 657–663.
14. Schwarz, K. 1965 Selenium and kwashiorkor. Lancet *1:* 1335.
15. Majaj, A. S., and L. L. Hopkins, Jr. 1966 Selenium and kwashiorkor. Lancet *2:* 592.
16. Thompson, J. N., and M. L. Scott 1970 Impaired lipid and vitamin E absorption related to atrophy of the pancreas in selenium-deficient chicks. J. Nutr. *100:* 797–809.
17. McCoy, K. E. M., and P. H. Weswig 1969 Some selenium responses in the rat not related to vitamin E. J. Nutr. *98:* 383–389.
18. Rotruck, J. T., A. L. Pope, H. E. Ganther and W. G. Hoekstra 1972 Prevention of oxidative damage to rat erythrocytes by dietary selenium. J. Nutr. *102:* 689–696.
19. Levander, O. A. 1971 Factors that modify the toxicity of selenium. In: Newer Trace Elements in Nutrition, pp. 57–83. Edited by W. Mertz and W. E. Cornatzer. Marcel Dekker, New York.
20. Parizek, J., I. Ostadalova, J. Kalouskova, A. Babicky and J. Benes 1971 The detoxifying effects of selenium. Interrelations between compounds of selenium and certain metals. In Newer Trace Elements in Nutrition, pp. 85–122. Editd by W. Mertz and W. E. Cornatzer. Marcel Dekker, New York.
21. Mason, K. E., and J. O. Young 1967 Effectiveness of selenium and zinc in protecting against cadmium-induced injury of the rat testis. In: Selenium in Biomedicine, ed., O. H. Muth. The AVI Publishing Co., Inc., Westport, Conn., pp. 383–394.
22. Scott, M. L., G. Olson, L. Krook and W. R. Brown 1967 Selenium-responsive myopathies of myocardium and of smooth muscle in the young poult. J. Nutr. *91:* 573–583.
23. Allaway, W. H., J. Kubota. F. Losee and M. Roth 1968 Selenium, molybdenum and vanadium in human blood. Arch. Environ. Health *16:* 342–348.
24. Nelson, A. A., O. G. Fitzhugh and H. O. Calvery 1943 Liver tumors following cirrhosis caused by selenium in rats. Cancer Res. *3:* 230–236.
25. Tinsley, I. J., J. R. Harr, J. F. Bone, P. H. Weswig and R. S. Yamamoto 1967 Selenium toxicity in rats. I. Growth and longevity. In: Selenium in Biomedicine, ed., O. H. Muth. AVI Publishing Co., Inc., Westport, Conn., pp. 141–152.
26. Harr, J. R., J. F. Bone, I. J. Tinsley, P. H. Weswig and R. S. Yamamoto 1967 Selenium toxicity in rats. II. Histopathology. In: Selenium in Biomedicine, ed., O. H. Muth. AVI Publishing Co., Inc., Westport, Conn., pp. 153–178.
27. Volgarev, M. N., and L. A. Tscherkes 1967 Further studies in tissue changes associated with sodium selenate. In: Selenium in Biomedicine, ed., O. H. Muth. AVI Publishing Co., Inc., Westport, Conn., pp. 179–184.

28. Schroeder, H. A., and Marian Mitchener 1971 Selenium and tellurium in rats: Effect on growth, survival and tumors. J. Nutr. *101:* 1531–1540.
29. Clayton, C. C., and C. A. Baumann 1949 Diet and azo dye tumors: Effect of diet during a period when the dye is not fed. Cancer Res. *9:* 575–582.
30. Weisberger, A. S., and L. G. Suhrland 1956 Studies on analogues of L-cysteine. The effect of selenium cystine on Murphy lymphosarcoma tumor cells in the rat. Blood *11:* 11–18.
31. Weisberger, A. S., and L. G. Suhrland 1956 Studies on analogues of L-cysteine. III. The effect of selenium cystine on leukemia. Blood *11:* 19–30.
32. Shamberger, R. J., and G. Rudolph 1966 Protection against cocarcinogenesis by antioxidants. Experientia *22:* 116–122.
33. Riley, J. F. 1969 Mast cells. Cocarcinogenesis and anticarcinogenesis in the skin of mice. Experientia *24:* 1237–1241.
34. Shamberger, R. J. 1970 Relationship of selenium to cancer. I. Inhibitory effect of selenium on carcinogenesis. J. Nat. Cancer Inst. *44:* 931–936.
35. Shamberger, R. J., and C. E. Willis 1971 Selenium distribution and human cancer mortality. In: Critical Reviews in Clinical Lab. Sciences, June 1971, pp. 211–221.
36. Scott, M. L., and J. N. Thompson 1971 Selenium content of feedstuffs and effects of dietary selenium levels upon tissue selenium in chicks and poults. Poultry Sci. *50:* 1742–1748.

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